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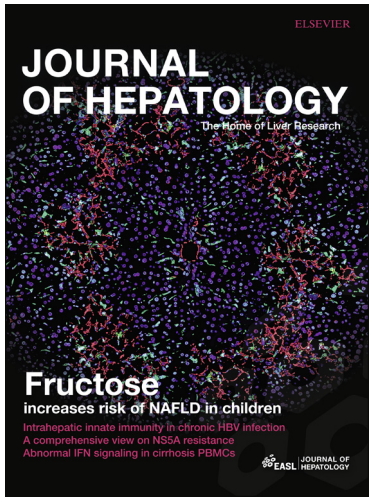

Letter to the Editor

Reply to: No effect of resistance-associated substitutions in patients with rare HCV subtypes following treatment with sofosbuvir-containing regimens

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Reply to: No effect of resistance-associated substitutions in patients with rare HCV subtypes following treatment with sofosbuvir-containing regimens

Ana da Silva Filipe[1], Vattipally Sreenu[1], Joseph Hughes[1], Elihu Aranday-Cortes[1], William L Irving[2], Graham R. Foster[3], Kosh Agarwal[4], William Rosenberg[5], Douglas Macdonald[5], Paul Richardson[6], Mark A. Aldersley[7], Martin Wiselka[8], Andrew Ustianowski[9], John McLauchlan[1], Emma C. Thomson[1]

1. MRC-University of Glasgow Centre for Virus Research, Glasgow, UK.
2. Gastrointestinal and Liver Disorders Theme, NIHR Nottingham Biomedical Research Centre at the Nottingham University Hospitals NHS Trust and the University of Nottingham, UK.
3. Blizard Institute, Queen Mary University of London, London, UK.
4. Institute of Liver Studies, King's College Hospital Foundation Trust, London UK.
5. Institute of Liver and Digestive Health, University College of London, London, United Kingdom.
6. Royal Liverpool University NHS Trust, Liverpool, UK.
7. Liver Unit, St James's University Hospital, Leeds, UK.
8. Infectious Diseases Unit, University Hospitals Leicester NHS Trust, Leicester, UK.
9. Infectious Diseases, North Manchester General Hospital, Manchester, UK.

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Correspondence: Prof J McLauchlan, MRC-University of Glasgow Centre for Virus Research, Sir Michael Stoker Building, Garscube Campus, Glasgow G61 1QH, UK; E-mail, john.mclauchlan@glasgow.ac.uk; Tel no. +44 141 330 4028.

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Author Contributions: The study was designed and led by AS, JM and ECT. EAC, VS and JH formed NGS and host genetic analysis. WLI collated and provided the clinical data from HCV Research UK. GRF, KA, WR, DM, PR, MAA, MW and AU consented the patients, provided clinical data and provided samples. All authors contributed to and commented on the drafting of the final manuscript.

To the Editor:

We thank Zeuzem *et al* for their response to our recently published findings (1, 2). Their data provide a valuable addition to reports describing virological outcomes for patients infected with "rare" subtypes who have received sofosbuvir (SOF)-based therapy but have not been well represented in previous large-scale clinical trials. We agree with the authors that assessing treatment outcome in cohorts infected with poorly characterized or uncharacterized subtypes would ideally be determined from patients who have achieved both SVR and treatment relapse. However, well-defined cohorts do not exist in most low- and middle-income countries (LMICs) where such subtypes are typically found, and consequently the necessary evidence base has been lacking.

We wish to comment further on the implications for treatment of patients in LMICs as part of the WHO global elimination plan. Recently, we published a study illustrating the lack of HCV sequence data in LMICs, particularly those in Africa as well as South and Central America (3). We agree that a SVR rate of 100% in 8 gt4r-infected patients treated with SOF/VEL±VOX is reassuring. However, the additional finding of SOF/LDV treatment failure in 2/4 patients with gt4r in Zeuzem *et al*'s larger analysis (1) is concerning although the authors did not give details of the disease status of these patients. In our study, all EAP patients had cirrhosis, which may well have influenced response to therapy. The apparent lower response of gt4r to SOF/LDV is worth highlighting for countries planning to use generic versions of these DAAs as treatment for gt4 infection where a significant proportion of patients are possibly infected with the gt4r subtype. Although gt4r is uncommon in Europe and the USA, it is not a rare genotype in Central African countries including the Democratic Republic of the Congo, the Republic of Congo, the Central African Republic, Burundi, and Gabon. It will be important for these countries to consider the potential advantage of using SOF/VEL-based treatment versus SOF/LDV to achieve high rates of HCV clearance.

Finally, the large dataset provided by Zeuzem *et al* substantially increases the available data for DAA target genes in subtypes that are rare in high income countries (HICs).

However, there remains a question as to whether the full extent of RAS polymorphisms in such subtypes should be considered as fully documented. Regarding gt1l, also associated with lower SVR rates in our study, we combined the sequence data for gt1l isolates across the HCV NS5A coding region between residues 24-32 where RAS typically occur from Zeuzem *et al*, our publication (Filipe *et al*) and available Genbank sequences. Our analysis shows that methionine is dominant at positions 28 and 31 (11/12 sequences). However, position 30 is polymorphic in gt1l (Q, n=7; R, n=5). In the common gt1 subtypes, gt1a and gt1b, position 30 does not show such variability; for gt1a, Q is encoded in 96% of sequences (4801/4983) and for gt1b, R is encoded in 92% of sequences (4328/4705) (McLauchlan, unpublished). The motif consisting of $M^{28}R^{30}M^{31}$ is found not only in gt1l but also gt4r. The gt1l-infected patients reported by Zeuzem *et al* who had this motif received VEL and not LDV, which was the prescribed NS5A inhibitor in our EAP cohort. We note that one of the gt4r-infected patients in the Zeuzem *et al* study with the $M^{28}R^{30}M^{31}$ motif did receive LDV and relapse occurred, the second patient who received LDV had a $V^{28}R^{30}M^{31}$ motif. All other gt4r-infected patients who achieved SVR received SOF/VEL±VOX. In the absence of relevant *in vitro* subgenomic replicons to test gt1l, we agree with Zeuzem *et al* that patients receiving SOF-based regimens for gt4r should be treated with VEL but this recommendation could be extended to geographic regions where gt1l may circulate to mitigate against possible resistance with strains containing the $V/M^{28}R^{30}M^{31}$ motif.

In summary, the available, modest data suggest that NS5A polymorphisms, which may impact treatment response are common in HCV strains from certain African genotypes. The impact of these polymorphisms appears to be minimal in patients receiving SOF/VEL-based regimens but there are concerns about the efficacy of LDV in these isolates. Further studies examining the effectiveness of current therapies in larger numbers of patients will be required to identify the optimum regimen for these potentially resistant subtypes.

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